OPERATING COSTS AND EQUIPMENT

PROGRAM

1. CONTRACTOR UNION CARBIDE CORPORATION NUCLEAR DIVISION	CONTRACT NO. W7405-eng-26	TASK NO.
2. PROJECT TITLE Inhalation toxicity of inorganic nickel compounds		189 NO.
3. BUDGET ACTIVITY NO.	4. DATE PREPARED	

5. METHOD OF REPORTING

- [ ] MONTHLY
- [ ] OPEN LITERATURE
- [ ] QUARTERLY
- [ ] TOPICAL
- [ ] SEMI ANNUAL
- [ ] OTHER *(Specify)*
- [ ] ANNUAL

6. WORKING LOCATION: OAK RIDGE, TENNESSEE

- [ ] X-10 SITE
- [ ] ORGDP SITE
- [ ] Y-12 SITE
- [ ] OTHER *(Specify)*
- [ ] MELTON VALLEY

7. PERSON IN CHARGE
H. P. Witschi, Biology

PRINCIPAL INVESTIGATOR(S)
H. P. Witschi
W. Dalbey

8. PROJECT TERM
FROM: TO:

- [x] NEW WORK
- [ ] ESTABLISHED PROGRAM

	FY 19		FY 19		FY 19	
9. PERSON-YEARS a) SCIENTIFIC	1.0					
b) OTHER TECHNICAL	2.0					
TOTAL	3.0					
10. FUNDING ($000) OPERATING COSTS:	B/A	B/O	B/A	B/O	B/A	
a) DIRECT SALARIES		76,000				
b) MATERIALS & SERVICES		53,000				
c) CAPITAL EQUIPMENT		35,000				
d) INDIRECT EXPENSES		39,990				
TOTAL OPERATING COSTS		203,990				
CAPITAL EQUIPMENT NOT RELATED TO CONSTRUCTION ($000)						

11. REACTOR CONCEPT N/A	12. MATERIALS N/A

13. DATES AND TITLES OF PUBLICATIONS:

New project - not applicable

14. SCOPE

The National Institute of Occupational Safety and Health has recently issued criteria for a recommended standard of occupational exposure to inorganic nickel (DHEW (NIOSH) Publication No. 77-164). It is the conclusion of this report that human exposure to airborne inorganic nickel may increase the risk to develop nasal and lung cancer. Evidence to support this view is provided in several usually well documented epidemiologic studies on nickel workers in various countries. On the other hand, experimental data in animals which would allow to define nickel unequivocally as a respiratory carcinogen are incomplete and not convincing. Nevertheless, NIOSH has concluded that, in the absence of evidence to the contrary, nickel metal and all inorganic nickel compounds, when airborne, should be considered carcinogens. These considerations led to the recommendation that a new standard for occupational exposure to nickel needs to be adopted. It is proposed that no worker should be exposed to nickel at a concentration greater than 15 μg, measured as nickel, per cubic meter of air, determined as time-weighted average concentration for up to a 10 hour work-shift, 40 hour work-week. Essentially, this represents the lowest reliably detectable concentration of nickel measurable by sampling and analytical methods selected and endorsed by NIOSH.

The experimental data in animals, which tend to implicate inorganic Ni compounds to be respiratory carcinogens, are summarized and tabulated in the NIOSH document. An examination of the data shows that only in 2 out of 5 studies published in the anglo-saxon literature there was evidence which could label inorganic Ni compounds to be a respiratory carcinogen. Out of the two studies, a quite old one (Hueper, 1958) does not provide all too convincing evidence; the study was analyzed in the NIOSH document and said to show only "suggestive lesions . . . (but) . . . no clear indication of carcinogenicity" (incidentally the study is plagued by inadequate controls). This leaves some recent experiments done by Ottolenghi et al (1973) as the only inhalation study where acceptable evidence for carcinogenesis by an inorganic Ni compound (Ni_3S_2) in the respiratory tract was obtained. On the other hand, the other 3 studies in which animals were exposed to inorganic Ni by either inhalation or intratracheal instillation failed to provide evidence for carcinogenicity.

It must be noted, however, that under different experimental conditions Ni has unequivocally been shown to be a carcinogen. For example, inhalation or injection of nickel carbonyl causes tumors in lung and other organs at low incidence. Intramuscular administration of various nickel salts produces sarcomata in high incidence. Topical application of microgram quantities to kidney produces malignant tumors. The carcinogenic potency of various Ni compounds appear to be inversely related to water solubility.

Information on "bioavailability" of Ni in target tissues could thus be an important factor when it comes to deciding whether there is a carcinogenic risk associated with different forms of airborne inorganic Ni compounds. By saying this we assume that, in order to be carcinogenic, Ni has to reach its presumptive target site in a high enough concentration, suitable chemical form and/or has eventually to persist. Viewed at it this way, it is fully conceivable that different forms of inorganic Ni could have different potencies for eliciting a malignant response.

It is the purpose of this program to examine this possibility more closely. For this we propose to collect systematically data on localization, translocati and finally elimination from the body of inorganic Ni compounds following uptak through the respiratory tract. At the same time, preliminary work will begin a at setting up conditions so that a chronic inhalation study could be started sh the need arise. The outline given below discusses the suggested approach in mo detail.

15. RELATIONSHIP TO OTHER PROJECTS:
Not applicable

16. TECHNICAL PROGRESS IN FY 1978:

New project

17. EXPECTED RESULTS IN FY 1979:

We plan to obtain information on the toxicokinetics of 3 insoluble and one solul Ni compound (i.e. metallic Ni, NiO, Ni_3S_2 and $NiCl_2$) in rats and possibly mice. The route of exposure will be through the respiratory tract. Uptake, retention translocation and elimination of Ni from the body will be measured. The data w allow to determine whether the fate of all these Ni compounds within the body i the same or whether there are differences in toxicokinetic behavior. Ultimatel such data may help to assess the relative risk each one of the compounds repres if humans are exposed by inhalation.

In order to facilitate analysis of tissue, we plan to work with radioactive Ni. Commercially available $^{63}NiCl_2$ will be converted with suitable preparative procedures into NiO, Ni_3S_2, metallic Ni or diluted with carrier $NiCl_2$.

The first step in the animal studies will be to administer the various Ni compo to rats by intratracheal instillation. Guidance as to what dosage levels to us will be taken from the literature whenever available. These experiments should provide preliminary information on how long Ni can be expected to be retained i appreciable amounts within the respiratory tract. The information is necessary for establishing exactly the specific activity of the Ni compounds to be admini in the subsequent inhalation experiments.

The second step will be to repeat the experiments, but this time by exposing th animals to radioactive Ni aerosols. To do this, we will need to take appropria precautions, which will allow us to expose animals without any risk to their handlers. Most probably, we will have to use a chamber constructed for nose-on exposure of animals. Such a small chamber can be placed within a larger, prope ventilated and filtered facility. This eliminates the risk that radioactive ae escapes from the inhalation area. Nose-only exposure has the additional advant that the animals' furs become only very little, if at all, coated with the test material. This minimizes uptake of Ni into the body by gastrointestinal absor following grooming. A disadvantage of the method is, however, that animals hav be bodily restrained in a nose-only inhalation chamber. This limits duration c exposure, in order not to stress the animals too much.

Ideally, we plan to expose the animals to 2 concentrations (low and high) of th test compounds and then to determine total lung burden of Ni immediately after exposure and on selected time points thereafter. In order to obtain the fullest possible information on tissue distribution, we plan to use whole-body autoradiograph In this method, animals are frozen in toto and embedded in carboxymethyl cellulose. With the help of a special cryomicrotome, sagittal sections (a few microns thick) of the whole animal body are cut, mounted on plastic film, covered with photographic emulsion, exposed for a suitable time and developed. Accumulation of radioactive Ni will be visualized by a blackening of the film. Quantitative information of the amount of Ni present in a given spot can be obtained by densitometry or, more accurately, by punching out the isotope-containing region and subseqeunt liquid scintillation counting. This method has a very crucial advantage over conventional analysis for radioactivity by collecting tissue samples at autopsy: it allows to obtain information on Ni distribution in the entire organism. With analysis of individual tissue, secured and selected at autopsy, there is a real risk that accumulation of Ni in small, but potentially critical areas may go undetected (e.g. specific regions of the brain, regional lymph nodes, small organs which may be overlooked such as hypophysis, ovaries, or transplacental passage of Ni to the fetus in pregnant animals).

These studies on accumulation and clearance of Ni following inhalation exposure can be extended, if necessary, to include studies on repeated and prolonged exposure. They can also be accompanied by conventional histopathologic studies of selected tissue samples.

The second major effort will be to develop techniques for chronic inhalation studies with inorganic Ni aerosols. These experiments will be done roughly in parallel with the studies on toxicokinetics. Essentially, conditions will be established which should allow to operate large inhalation chambers (1.5 m^3) with aerosols of Ni, NiO, Ni_3S_2 and $NiCl_2$ of known concentrations. The first step will be to ascertain that it is possible to produce and reproduce the aerosols. In any such study, particle size is of critical importance. It will be necessary to create dusts containing a known proportion of respirable particles, comparable to situations encountered in human exposure or in earlier studies reported in the literature. The next step will be to provide a reliable monitoring system and also to ascertain that we can vary particle concentrations over a wide range of doses. Aerosol generation and particle/concentration monitoring will be done following established procedures.

Once conditions are established, we plan to do some dose-finding studies, using a limited number of animals. To do subacute and chronic inhalation studies with Ni compounds, the established procedure would be to determine, in acute experiments, a maximum tolerated dose (MTD). However, it is evident from data in the literature and also from personal communications of investigators involved in Ni inhalation studies, that inorganic Ni is very little toxic to small rodents, even if atmospheres as high as 200 mg/m^3 are generated. This necessitates that studies are done in which animals will be exposed to doses of Ni used in studies by previous investigators (i.e. 1 mg/m^3) as well as higher concentrations (up to possibly 20-80 mg/m^3). Again, animals would be exposed to the different compounds and observations be made on acute toxicity, acute accumulation of Ni in lung and on acute histopathological changes. The data could serve as preliminary information for possible exposure schedules in future chronic inhalation toxicity studies.

In conclusion, the suggested studies are designed to provide data on accumulation, distribution and clearance of various forms of inorganic Ni following inhalation. They might help to estimate possible risks for each compound. Also, preliminary work will be done which will help to validate techniques and to define conditions to be used in eventual later chronic inhalation studies.

19. DESCRIPTION, JUSTIFICATION, AND COSTS OF MAJOR MATERIAL, SUBCONTRACTS, TECHNICA SERVICES, COMPUTER AND PROGRAMMING AND CAPITAL EQUIPMENT OBLIGATIONS.

	Cost Estimates	
	FY 1979	FY 1980
Capital Equipment Obligations		
LKB Cryo-microtome	35,000	

This is a special instrument, not available in the Biology Division, which will allow to prepare whole-body autoradiograms. The cost is included in the operating budget presented on page 1.

20. PROPOSED OBLIGATIONS FOR RELATED CONSTRUCTION PROJECTS, IF ANY:

None strictly for this program.